Response of Metal Carboxylates Coalition
To
EPA Comments on Chemical RTK HPV Challenge Submission:
Calcium dipropionate

SUMMARY OF EPA COMMENTS WITH RESPONSES (in italics)

The sponsor, the Metal Carboxylates Coalition ("the Coalition), submitted a revised test plan and robust summaries to EPA for Calcium dipropionate (CAS No. 4075-81-4), dated September 10, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 22, 2004. Data were also submitted for a proposed analog, propionic acid (CAS No. 79-09-4).

EPA has reviewed this submission and has reached the following conclusions and made the following recommendations. Where conclusions required additional information and were addressed by the Coalition, such as modifications of the robust summaries or test plan a summary of each action is provided in italics beneath each conclusion.

1. Environmental Fate. EPA states that the Coalition needs to provide Model III fugacity results for propionic acid.

The Coalition provides Model III fugacity results for Ca dipropionate and propionic acid. The Ca dipropionate data is provided in the robust summaries and the propionic acid data is presented in the remarks section of the robust summary section 3.3.1 Transport (Fugacity). Results are discussed in the test plan.

4. Health Effects. EPA has reserved judgment on the adequacy of the reproductive and developmental toxicity endpoints pending submission of information on the reproductive organs evaluation from an adequate repeated-dose toxicity study and a justification for dose selection for the developmental toxicity studies.

An additional study to obtain data for repeated dose or developmental endpoints is unnecessary for the following reasons:

- *The rationale for choosing a lower maximum dose in the developmental study is not clear. The Coalition believes the developmental study conducted in 1972 by the Food and Drug Research Laboratories (FDRL) on contract from the Food and Drug Administration is reliable with restrictions. FDRL had a good reputation and based on the information in the study report this was a well conducted study. The conduct of this study preceded the time when the 1,000 mg/kg/d dose level became standard practice. This study was supported by four additional studies with a total of five species with lower exposure levels.*

- *Ca and propionate are both natural constituents of human and animal metabolism. Ca dipropionate has been used for many years as a feed additive in cattle to promote blood calcium levels. All life stages of cattle are exposed including treatment of dams during pregnancy and after calving. Young calves receive as much as 60g/kg/d for up to six weeks with no deleterious effects (Spears et al. 2003, Bunting et al. 2000). With this extensive level of use on a broad scale any adverse effects from repeated dose or developmental problems would have been observed by the cattle producers who carefully observe their animals to promote good health and growth.*

- *In requesting additional developmental data the EPA must consider the number of additional animals needed to conduct such a study. A minimum of 88 animals would be*

(OECD 421). The Coalition believes this would be an unnecessary use of animals and is inconsistent with animal welfare concerns.

EPA COMMENTS ON THE CALCIUM DIPROPIONATE CHALLENGE SUBMISSION

Test Plan

Environmental Fate (photodegradation, stability in water, biodegradation and fugacity)

The data provided for the photodegradation and biodegradation endpoints are adequate for the purposes of the HPV Challenge Program.

Stability in water. The dissociation data provided by the Coalition are adequate for the purposes of the HPV Challenge Program, if augmented with a robust summary for the stability constant data in Furia (1972).

Insufficient data is available in Furia (1972) and a robust summary cannot be provided.

Fugacity. The Coalition needs to provide level III fugacity modeling data for propionic acid. A Henry's Law constant alone is not sufficient.

The Coalition provides Model III fugacity results for propionic acid and Ca dipropionate. The Ca dipropionate data is provided in the robust summaries and the propionic acid data is presented in the remarks section of the robust summary section 3.3.1 Transport (Fugacity). Results are discussed in the test plan.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data for acute, repeated-dose and genetic toxicity endpoints are adequate for the purposes of the HPV Challenge Program. EPA reserves judgment on the adequacy of the reproductive and developmental toxicity endpoints pending submission of information on the reproductive organs evaluation from an adequate repeated-dose toxicity study and a justification for dose selection for the developmental toxicity studies.

Reproductive/Developmental toxicity. No reproduction toxicity studies have been conducted with Ca dipropionate. EPA agrees that the results of repeated-dose toxicity studies and available developmental toxicity studies should address these endpoints. However, (1) none of the robust summaries for repeated-dose toxicity studies provides a list of reproductive organs that were weighed and/or evaluated histopathologically and (2) the dose levels used in the developmental toxicity studies were significantly lower (300-400 mg/kg/day) than recommended (1000 mg/kg/day) for this type of study by the OECD guidelines. Because neither maternal nor developmental toxicity was evident at these doses, a justification for dose selection is needed.

See responses above (4. Health Effects).

Specific Comments on the Robust Summaries

Environmental Fate

Stability in water. The Coalition needs to rename Section 3.1.2 in the IUCLID Data Set for calcium propionate as "Stability in Water – Dissociation".

> *The title of Section 3.1.2 of the robust summary was changed to "Stability in Water – Dissociation".*

Health Effects

In the IUCLID Data Set for propionic acid, calcium salt, the submitter needs to prepare and incorporate an individual robust summary for each study discussed in the additional references sections. Section 5.11 of the IUCLID Data Set for propionic acid, which is not essential for this submission, needs to be translated into English or deleted.

> *The additional reference sections of this document are unnecessary and were deleted. The Section 5.11 was also deleted from the robust summaries.*

Genetic toxicity (gene mutations). Missing robust summary information includes: identity of the positive controls used, criteria used to evaluate a positive or negative response, detailed description of the method.

> *The missing data was added to robust summary including identity of the positive controls, criteria used to evaluate a positive or negative response, and detailed description of the method.*

Reproductive toxicity. Histopathological data relating to the reproductive organs from the repeated-dose studies need to be included in this section.

> *Histopathology data does not exist for the current repeated dose or the developmental studies.*

References

Bunting, L.D., T.A. Tarifa, B.T. Crochet, J.M. Fernandez, C.L. Depew and J.C. Lovejoy. 2000. Effects of dietary inclusion of chromium propionate and calcium propionate on glucose disposal and gastrointestinal development in dairy calves. J. Dairy Sci 83:2491-2498.

Furia, T.E 1972. Sequestrants in foods. In *CRC* Handbook of Food Additives, 2nd ed. Online at http://www.coldcure.com/html/stability_constants.html.

Spears, J.W., T.E. Engle, W.R. Platter, and K.E. Lloyd. 2003. Effects of high dietary calcium propionate and a dietary cation-anion balance on calcium metabolism and longissimus muscle tenderness in finishing steers. Professional Animal Scientist December 2003.